NAPM

NATIONAL ASSOCIATION OF PHARMACEUTICAL MANUFACTURERS
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March 24, 1999

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rrn 1061
Rockville, MD 20852

RE: Docket No. 98D-1195 - Guidance for Industry -- Bioanalytical Methods Validation for Human Studies

The National Association of Pharmaceutical Manufacturers (NAPM) appreciates the opportunity to comment on the document, "Guidance for Industry: Bioanalytical Methods Validation for Human Studies " [Docket No. 98D-1195]. These comments represent the consensus of our members including our contract research organization (CRO) subcommittee.

We are very pleased that the Agency has produced a document that provides guidance for bioanalytical methods validation. We appreciate that the guidance, for the most part, follows the industry approach for performing bioanalyses.

NAPM is the national trade organization representing manufacturers, distributors and repackagers of generic multisource prescription drugs, OTC drugs, dietary supplements and veterinary drugs. The organization prides itself in serving the needs of its members and has been heavily involved in legislative, legal, regulatory and technical issues.

We thank you for the opportunity to submit our comments. We hope that our comments are clear and welcome any questions that you may have. Moreover, we hope that as experience is gained with this document, the guidance will be revised accordingly.

Sincerely,

Leon Shargel

Leon Shargel, Ph.D.
Vice President and Technical Director

cc: Vinod Shah, Ph.D.

98D-1195

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GUIDANCE FOR INDUSTRY
BIOANALYTICAL METHODS VALIDATION FOR HUMAN STUDIES
DOCKET NO. **98D-1195**

GENERAL COMMENTS:

A guidance describing bioanalytical methods validation has been needed by the industry. However, there are several areas in the guidance that need clarification. For example, immunochemistry methods require a different approach to bioanalytical validation compared to the more 'classical' chemical approach to bioanalytical validation.

In addition, the draft guidance does not clearly differentiate as to when a limited or full validation is required. Our interpretation is that minor modifications to the method may not have more than a minor impact on the method. Only small changes in the parameters listed in the Guidance require limited validation. Limited validation includes precision and accuracy (within and between batch), specificity, and recovery.

Larger changes in these parameters require full validation except for stability. However, any changes in the method that impact on the stability of the compound of interest would require reassessment of the stability. In addition, a change of detector or instrument technology (e.g. LCMS to GC/MS, or electronic multiplier to fluorescence) would necessitate full validation including stability.

The documentation requirement for including all SOPS, raw data, calculations of concentration, and reassay sample sets puts an additional burden on the analytical laboratory. We recommend that all documentation appropriate to the study be made available to the Agency at an audit of the bioanalytical laboratory. The inclusion of all SOPS and other supporting documentation will add hundreds of pages of documents in each study report and a redundancy of effort for each submission.

SPECIFIC COMMENTS:

p. 2, III. REFERENCE STANDARD

While it is desirable to have a Master reference standard for each assay validation, storage conditions or issues of stability may render the Master standard invalid. Evidence as to the identity and purity should be all that is required for the Reference standard. Once fully certified, the Reference standard and subsequent batches can replace the Master standard.

p. 4, IV.A. Specificity, paragraph 2

Any blank sample with significant interference at the retention time of the drug, metabolizes, or internal standard should be rejected. If more than 10% *of the blank samples exhibit significant interference at these retention times, additional matrix blank samples should be tested. If more than 10% of this subsequent group of blank samples still shows inter ference, the method should be changed to eliminate the interference.*

Comment:

The guidance recommends that 6 individual lots of blank matrix are be tested for interference (p. 3). In this paragraph, cited above, if more than 10°/0 show significant interference then additional matrix blank should be tested. However, a single blank sample that shows significant interference at the retention time of the drug, metabolites, or internal standard would account for 1/6 of the total samples (which is >lO°/O). The criteria are not compatible.

The guidance should indicate that if one of the six blank samples show interference, then additional matrix blanks may be used and no more than 10°/0 of the additional matrix blanks may show interference.

pp. *3-4*, IV.A. Specificity

The results should be compared to those obtained with an aqueous solution of the analyte at a concentration near the limit of quantitation (LOQ).

Comment:

Change this sentence to read: "The results should be compared to those obtained from an extracted sample of the analyte(s) in matrix, at a concentration near the limit of the quantitation (LOQ)".

Rationale - The response from an aqueous solution of the analyte may be different from that of the analyte in matrix (the possibility of ion suppression or matrix effect).

p. *4*, IV.A. Specificity, paragraph 3

The recommendation in paragraph three, to assess potential interference from nicotine and common OTC drugs and metabolizes is neither practicable nor a realistic procedure for all methods. Some compounds which might interfere chromatographically may be excluded based upon the polarity of the compounds and extraction procedure (i.e. acidic compounds extracted under basic conditions).

p. 5, IV. B. 2. Linearity

The simplest workable regression equation should be used with minimal or no weighting.

Comment:

The sentence could be changed to read: "The ~~simplest~~ best workable regression equation should be used with minimal or no weighting"

Rationale - Since system response influences the regression equation, the most appropriate regression equation should be used for a particular method. For example, Dr. E. Kimanami, Phoenix International Life Sciences presented to the FDA Office of Generic Drugs on 17 October 1996, a more objective tool to determine the best fit achievable. This power model may be a more objective method of establishing the best workable equation.

p. 5, IV. B. 2. Linearity

- *At least four out of six non-zero standards meeting the above criteria, including the LOQ and the calibration standard at the highest concentration.*

Comment:

We recommend that the bullet be changed to read "At least two thirds of the non-zero standards meeting the above criteria including the LOQ and the calibration standard at the highest concentration. "

Rationale - This statement requires clarification since the sentence is contradicted on page four by the requirement of 5 to 8 non-zero standards for a calibration curve. Also, we request clarification of this statement. In addition, the sentence is unclear if "outliers" can be discarded from the calculations provided four of six non-zero standards including the LOQ and the calibration standard at the highest concentration (ULQ) are included.

Please note that the criteria requiring both the LOQ and the ULQ is too strict for immunochemistry methods.

p. 5, IV. B. 2. Linearity

- 0.95 *or greater correlation coefficient (r)*

Comment:

We consider that an r value (correlation coefficient) of 0.95 to be too low and recommend an r value of 0.99.

p. 5, IV. C. Precision, Accuracy and Recovery

Comments:

The Guidance should be more specific regarding terminology. There can be a difference between intra-day and intra-batch. A laboratory may analyze several batches in one day by using several instruments (common for large studies). The same may take place during pre-study validation.

The precision of 15% required for each QC, and 20% for the LOQ in validation is not consistent with the criteria for in-study validation (section V. In-Study Validation, paragraph 4, sentence five) of at least four of six QC samples within (20% of their respective nominal value.

p. 6, IV. C. Precision, Accuracy and Recovery, paragraph 2

Although recoveries close to 100% are desirable, the extent of recovery of an analyte and/or the internal standard may be as low as 50 to 60% if the recovery is precise, accurate, and reproducible.

Comment:

The sentence be modified to read as follows: "Although recoveries close to 100% are desirable, a lower recovery of an analyte and/or internal standard is acceptable."

Rationale - The focus of assay development is the establishment of an accurate, precise and sensitive method with good selectivity and not necessarily a high recovery.

p. 6. IV. D. Quality Control Samples

If each set of QCS prepared from a separate source of matrix are run against a standard curve prepared from the same batch matrix lot, differences in response due to matrix effect would not be discernible. It is advantageous to look at a matrix effect; however, the high and low QCS should be prepared for each of 6-10 donors (minimum of 6) and run against one standard curve. In this way, any difference in response in the QCS due to matrix effect would be observable.

LOQ QC sample: concentration same as lowest non zero standard and prepared from a stock solution separate form that used to prepare the standards. Is there any degree of variation allowed? Might a tolerance of the LOQ QC concentration be +/- 20°/0? The LOQ QC is run during validation to establish the precision and accuracy at the LOQ not to evaluate the error due to weighing. Therefore, the LOQ QC can be prepared from the same stock as the standards. The error due to weighing can be adequately assessed with the three other levels of QC concentration.

Low QC sample: The range of ≤3 x LOQ might be appropriate for standard curves with relatively small ranges. However, if the range from lowest standard to highest standard is great, you risk having 2 QCS at the very bottom of the curve and not nicely distributed over the entire range.

We recommend that an alternative to using the "theoretical" concentration should be to use the actual concentration found after analysis of 9 replicates for each QC. This would allow for the acceptance of QC'S with minor spiking errors.

p. 7, IV. E. 1. Freeze and Thaw Stability

The guidance indicates samples should be thawed "unassisted" at room temperature. For freeze and thaw stability, stability samples should mimic standard assay conditions. This may not always consist of thawing unassisted at room temperature.

p. 8, IV. E. 4. Stock Solution Stability

The conditions of storage may not always be room temperature for stock stability. Our recommendation is that the assessments for freeze and thaw and stock stability contain the statement that stability samples be subjected to conditions that are identical to those expected for the study sample conditions. If subject samples are thawed at 30 degrees C, then freeze-thaw should be done in the same manner.

p. 8, IV. E. 5. Autosampler Stability

Short-term stability assessment can establish stability for the time thesamples arein the autosampler at room temperature, Our recommendation is that autosampler stability only be performed when conditions in the autosampler are different from room temperature.

p. 9, IV. F. Acceptance Criteria

This section does not mention of the criteria for the calibration curve.

Stability: *Long-term, short-term, freeze and thaw, stock solution, and autosampler stability data should meet the criteria specified in the SOP.*

Comment:

The criteria for stability should not be left open, but should be assessed using a simple statistical analysis of the stability and the freshly prepared samples to determine that these are not two distinct populations. An example of a statistical approach to evaluate stability values versus those obtained for the freshly prepared comparison samples was published (Timm, U., M. Wall, and D. Dell, "A New Approach for Dealing with the Stability of Drugs in biological Fluids," J Pharm Sci 1985; 74: 972-977).

p. 10, p. VI. Documentation

Paragraph two: The suggestion that re-assays are to be done in triplicate is unclear. Does that include the original analysis of the sample? Although we agree with the process to obtain the sample value closest to the true value, we feel that re-assays in triplicate may not be possible due to limitations of sample volume. We recommend that a policy that clearly defines the rationale for repeat assays whether for samples lost in processing or due to anomalous values be written and followed rather than a blanket requirement that all repeats be done in triplicate. Also, there should be a recommendation of which value to report for the re-assayed samples.

Paragraph three: As data printed directly from instruments can not be recorded into bound laboratory notebooks, and as there are adequate alternatives to bound laboratory notebooks, we feel that this section should allow alternatives.

p. 12, D. VI. Documentation

- All SOPS, raw data, calculations of concentration, and reassay sample sets.

Comment:

The inclusion of all these documentation puts an additional burden on the analytical laboratory. SOPS, raw data, calculations of concentration, and reassay sample set are available for inspection.

We recommend that all SOPS only be referenced in the documentation. Hard copies or electronic copies of proprietary SOPS should not be a required part of a submission to the Agency. We recommend that all SOPS be made available to the Agency at an audit of the bioanalytical laboratory. The inclusion of the SOPS will add hundreds of pages of documents in each study report and a redundancy of effort for each submission.

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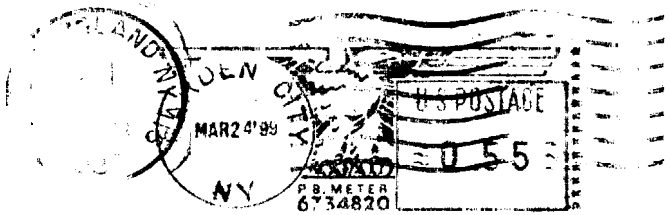

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